This rejection under 35 U.S.C. §112, first paragraph, appears to be a rejection for lack of written description. Applicants will consider this to be the nature of the rejection unless the Examiner advises otherwise.

Applicants have discovered a method of inhibiting histone deacetylase activity in cells. The method includes contacting the cells with an effective amount of a compound and determining whether the level of acetylated histones in the treated cells is higher than in untreated cells under the same conditions. See independent claim 1. See also page 2, lines 9-13 of the specification. As described in the specification, Examples 28-31 relate to inhibiting histone deacetylase activity. The specification specifically describes the utility of the claimed invention. The specification, including the Examples, describes the method of claim 1, and claims dependent therefrom as well. Indeed, one of ordinary skill in the art would understand the utility of the method of claim 1, and would find a written description of that method in the specification.

A detailed explanation of why the claimed invention has no specific and substantial credible utility was not provided with the rejection. Applicants believe that the "Guidelines for Examination of Applications for Compliance with the Utility Requirements" recited in MPEP 2107. Specifically, a *prima facie* showing that the claimed invention lacks utility has not been presented. MPEP 2107.02(IV) states:

> The *prima facie* showing must be set forth in a well-reasoned statement. Any rejection based on lack of utility should include a detailed explanation why the claimed invention has no specific and substantial credible utility. Whenever possible, the examiner should provide documentary evidence regardless of publication date (e.g., scientific or technical journals, excerpts from treatises or books, or U.S. or foreign patents) to support the factual basis for the *prima facie* showing of no specific and substantial credible utility. If documentary evidence is not available, the examiner should specifically explain the scientific basis for his or her factual conclusions.
>
> Where the asserted utility is not specific or substantial, a *prima facie* showing must establish that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial. The *prima facie* showing must contain the following elements:
>
> (A) An explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is neither both

specific and substantial nor well-established;

(B) Support for factual findings relied upon in reaching this conclusion; and

(C) An evaluation of all relevant evidence of record, including utilities taught in the closest prior art.

Where the asserted specific and substantial utility is not credible, a *prima facie* showing of no specific and substantial credible utility must establish that it is more likely than not that a person skilled in the art would not consider credible any specific and substantial utility asserted by the applicant for the claimed invention. The *prima facie* showing must contain the following elements:

(A) An explanation that clearly sets forth the reasoning used in concluding that the asserted specific and substantial utility is not credible;

(B) Support for factual findings relied upon in reaching this conclusion; and

(C) An evaluation of all relevant evidence of record, including utilities taught in the closest prior art.

Where no specific and substantial utility is disclosed or is well-established, a *prima facie* showing of no specific and substantial utility need only establish that applicant has not asserted a utility and that, on the record before the examiner, there is no known well-established utility.

It is imperative that Office personnel use specifity in setting forth and initial rejection under 35 U.S.C. 101 and support any factual conclusions made in the *prima facie* showing.

By using specificity, the applicant will be able to identify the assumptions made by the Office in setting forth the rejection and will be able to address those assumptions properly.

w/d

Accordingly, Applicants respectfully request reconsideration and withdrawal of the lack of utility and the lack of written description rejections.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 4-7, 10, 12, 17-18 and 40-46 have been rejected under 35 U.S.C. § 112, first paragraph,

> because the specification, while being enabling for some types of cancer, does not reasonably provide enablement for 'treating cancer' in general. The specification does not enable any person of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. ... The Skilled

> Artisan would view cancer as a group of maladies not treatable with one medicament or therapeutic agent (pages 4-5 of the Office Action).[1]

As noted above, Applicants have discovered a method of inhibiting histone deacetylase activity in cells. The method includes **contacting the cells with an effective amount of a compound** and **determining whether the level of acetylated histones in the treated cells is higher than in untreated cells under the same conditions**. See independent claim 1 and page 2, lines 9-13 of the specification. The specification, including the Examples 28-31, relate to and describe inhibiting histone deacetylase activity with compound of formula (I). One of ordinary skill in the art reading the specification would understand how to contact cells with an effective amount of a compound, and determine whether the level of acetylated histones in the treated cells is higher than in untreated cells under the same conditions. See, for example, Example 31 of the specification. Undue experimentation is not required to carry out either contact the cells with an effective amount of a compound or determine whether the level of acetylated histones in the treated cells is higher than in untreated cells under the same conditions.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the lack of enablement rejection. w/d ?

Rejection under 35 U.S.C. § 103(a)

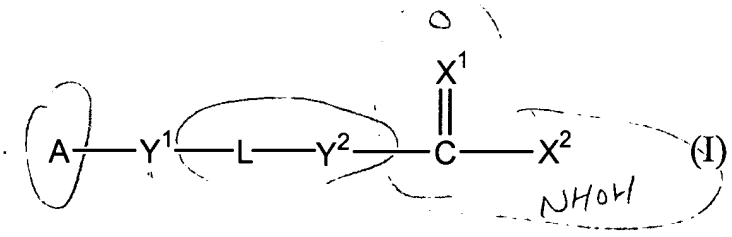
Claims 1, 2, 4-7, 10, 12, 17-18 and 40-46 have been rejected as under 35 U.S.C. § 103(a) as being unpatentable over Richon *et al.*, *Proc. Nat. Acad. Sci.* 95(6):3003-7 (1999) ("Richon") and Marks *et al. J. Nat. Cancer Inst.* 92(5):1210-6 (2000) ("Marks"). See pages 5-6 of the Office Action. As stated in the Office Action,

> Marks et al. teaches that hydroxamic-acid-based HPCs are potentially effective agents for cancer therapy, see abstract (reference FF of IDS).
>
> Richon et al. and Marks et al. do not explicitly teach the elected compound in their method of treating cancer.
>
> It would have been obvious to one of ordinary skill in the art at the time the invention was to employ the elected compound in a method of treating cancer.
>
> One of ordinary skill in the art would have been motivated to employ the elected compound in a method of treating cancer because the

[1] *In re Bunting*, 163 USPQ 689 (1969) is cited to support the lack of enablement rejection. However, *In re Bunting* relates only to assessing the utility of a claimed invention. Thus, *In re Bunting* is inapposite.

> elected compound is a hydroxamic acid derivative. The Skilled Artisan would reasonably expect the elected compound, a derivative of hydroxamic acid to exhibit therapeutic effects similar to hydoxamic [sic] acid because structurally related compounds would have been expected to have similar therapeutic effects (page 6 of the Office Action).

As described above, Applicants have discovered a method of inhibiting histone deacetylase activity in cells that includes **contacting the cells with an effective amount of a compound of formula (I)** and **determining whether the level of acetylated histones in the treated cells is higher than in untreated cells under the same conditions**. The compound of formula (I) is:



wherein A is a cyclic moiety selected from the group consisting of C_{3-14} cycloalkyl, 3-14 membered heterocycloalkyl, C_{4-14} cycloalkenyl, 3-8 membered heterocycloalkenyl, aryl, or heteroaryl; the cyclic moiety being optionally substituted with alkyl, alkenyl, alkynyl, alkoxy, hydroxyl, hydroxylalkyl, halo, haloalkyl, amino, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, alkylsulfonylamino, aminosulfonyl, or alkylsulfonyl; or A is a saturated branched C_{3-12} hydrocarbon chain or an unsaturated branched C_{3-12} hydrocarbon chain optionally interrupted by -O-, -S-, -N(R^a)-, -C(O)-, -N(R^a)-SO_2-, -SO_2-N(R^a)-, -N(R^a)-C(O)-O-, -O-C(O)-N(R^a)-, -N(R^a)-C(O)-N(R^b)-, -O-C(O)-, -C(O)-O-, -O-SO_2-, -SO_2-O-, or -O-C(O)-O-, where each of R^a and R^b, independently, is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxylalkyl, hydroxyl, or haloalkyl; each of the saturated and the unsaturated branched hydrocarbon chain being optionally substituted with alkyl, alkenyl, alkynyl, alkoxy, hydroxyl, hydroxylalkyl, halo, haloalkyl, amino, alkylcarbonyloxy, alkyloxycarbonyl, alkylcarbonyl, alkylsulfonylamino, aminosulfonyl, or alkylsulfonyl; each of Y^1 and Y^2, independently, is -CH_2-, -O-, -S-, -N(R^c)-, -N(R^c)-C(O)-O-, -O-C(O)-N(R^c)-, -N(R^c)-C(O)-N(R^d)-, -O-C(O)-O-, or a bond; each of R^c and R^d, independently, being hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxylalkyl, hydroxyl, or haloalkyl; L is a straight C_{2-12} hydrocarbon chain optionally

containing at least one double bond, at least one triple bond, or at least one double bond and one triple bond; said hydrocarbon chain being optionally substituted with C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, hydroxyl, halo, amino, nitro, cyano, C_{3-5} cycloalkyl, 3-5 membered heterocycloalkyl, monocyclic aryl, 5-6 membered heteroaryl, C_{1-4} alkylcarbonyloxy, C_{1-4} alkyloxycarbonyl, C_{1-4} alkylcarbonyl, or formyl; and further being optionally interrupted by -O-, -N(R^e)-, -N(R^e)-C(O)-O-, -O-C(O)-N(R^e)-, -N(R^e)-C(O)-N(R^f)-, or -O-C(O)-O-; each of R^e and R^f, independently, being hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxylalkyl, hydroxyl, or haloalkyl; X^1 is O or S; and X^2 is -OR^1, -SR^1, -NR^3-OR^1, -NR^3-SR^1, -C(O)-OR^1, -CHR^4-OR^1, -N=N-C(O)-N(R^3)$_2$, or -O-CHR^4-O-C(O)-R^5, where each of R^1 and R^2, independently, is hydrogen, alkyl, hydroxylalkyl, haloalkyl, or a hydroxyl protecting group; R^3 is hydrogen, alkyl, alkenyl, alkynyl, alkoxy, hydroxylalkyl, hydroxyl, haloalkyl, or an amino protecting group; R^4 is hydrogen, alkyl, hydroxylalkyl, or haloalkyl; R^5 is alkyl, hydroxylalkyl, or haloalkyl; and provided that when L is a C_{2-3} hydrocarbon containing no double bonds and X^2 is -OR^1, Y^1 is not a bond and Y^2 is not a bond; or a salt thereof. The method treats one or more disorders mediated by histone deacetylase. See independent claim 1.

Neither Richon nor Marks, nor their combination, describe or suggest a method of inhibiting histone deacetylase activity in cells that includes **contacting the cells with an effective amount of a compound of formula (I)** and **determining whether the level of acetylated histones in the treated cells is higher than in untreated cells under the same conditions**. Richon describes the compounds suberoylanilide hydroxamic acid (SAHA) and m-carboxycinnamic acid bishydroxamide (CBHA). These compounds are not compounds included in claim 1. Marks also describes histone deacetylase inhibitors, but none of the compounds disclosed therein (see Figure 3) are compound included in claim 1. Indeed, contrary to the assertion made in the Office Action, Richon does not suggest any modifications of SAHA or CBHA, and Marks does not suggest any modifications of the compounds disclosed in Figure 3. Neither Marks nor Richon provide any motivation to modify the compounds disclosed in the references. Thus, Marks and Richon, taken together or separately, do not teach or suggest the method of independent claim 1. Claim 1, and claims that depend from claim 1 are patentable over Marks and Richon.

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of this rejection.

CONCLUSIONS

Applicant asks that all claims be allowed. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 2-6-02

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